# Efficacy of immunotherapy in seropositive and seronegative putative autoimmune autonomic ganglionopathy

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## ABSTRACT

**Objective:** To evaluate the efficacy of immunotherapy in the treatment of patients with seropositive and seronegative putative autoimmune autonomic ganglionopathy (AAG) using validated autonomic function tests and instruments.

**Background:** AAG is an immune-mediated disorder characterized by prominent and selective involvement of autonomic nerve fibers or ganglia. Treatment with IV immunoglobulin (IVIg) or plasma exchange (PE) has been reported to be effective in single case reports.

**Methods:** We studied six patients, four with seropositive and two with seronegative putative AAG, who underwent autonomic function tests and completed two validated questionnaires, to assess autonomic symptoms before and after immunomodulatory treatment. Patients were treated with standard doses of IVIg, PE, or immunosuppressants in a specific sequential therapy protocol depending on clinical response.

**Results:** Of the six patients (all women, mean ages 49.3 ± 10.6 years), four patients were ganglionic ($\alpha$3) AChR autoantibody positive and two were autoantibody negative. All patients showed clinical improvement after treatment. Sudomotor function assessed by quantitative sudomotor axon reflex test and thermoregulatory sweat test improved in four patients after treatment.

**Conclusions:** Immunomodulatory treatment can be effective in both seropositive and seronegative putative autoimmune autonomic ganglionopathy. Plasma exchange or combined therapy with immunosuppressive agents should be considered in patients who do not benefit from IV immunoglobulin alone. *Neurology*® 2009;72:2002–2008

## GLOSSARY

**AAG** = autoimmune autonomic ganglionopathy; **AB** = ganglionic $\alpha_3$ acetylcholine receptor antibody; **AChR** = acetylcholine receptor; **AE** = antecedent event; **ASP** = autonomic symptom profile; **Aza** = azathioprine; **BP** = blood pressure; **CASS** = Composite Autonomic Severity Score; **CCS** = COMPASS Change Score; **COMPASS** = Composite Autonomic Symptom Score; **GI** = gastrointestinal; **$HR_{-db}$** = heart rate response to deep breathing; **IVIg** = IV immunoglobulin; **LGI** = lower gastrointestinal tract symptoms; **Myc** = mycophenolate mofetil; **OI** = orthostatic intolerance; **OH** = orthostatic hypotension; **NA** = not applicable; **NCS** = nerve conduction studies; **PE** = plasma exchange; **QSART** = quantitative sudomotor axon reflex test; **TST** = thermoregulatory sweat test; **UGI** = upper gastrointestinal tract symptoms; **VR** = Valsalva ratio.

Autoimmune autonomic ganglionopathy (AAG) is characterized by prominent and selective involvement of the peripheral autonomic nervous system due to an autoimmune process.[1] Patients typically develop generalized autonomic failure including orthostatic hypotension, anhidrosis, and parasympathetic dysfunction. The onset can be acute, subacute, or gradual.[1-3] The course is variable, with spontaneous improvement occurring in about one-third of patients,[1] but recovery is typically incomplete.

In about 50% of patients with AAG, ganglionic ($\alpha$3-type) acetylcholine receptor (AChR) autoantibodies are detected in high titers.[4] Antibody levels correlate with the severity of

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*Medications and Medical Devices:* A list of medications and medical devices used in this study is provided at the end of the article.

**Table 1** Clinical and autonomic characteristics at baseline

| Patient | Sex/age, y | AB | AE | Onset* | Weight loss/other clinical features | OI/OH | Sicca† | Pupil abnormal | UGI | LGI‡ | Bladder | CN§ | CASS | COMPASS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F/41 | + | N | Gradual | None | OI | 3 | Y | Y | 1 | N | Y | 3 mild | 92.39 |
| 2 | F/36 | + | N | Subacute | Weight loss 82 pounds | OH | 3 | Y | Y | 2 | Y | Y | 9 severe | 68.5 |
| 3 | F/65 | + | N | Gradual | None | OH | 2 | N | N | 1 | Y | N | 6 moderate | 62.83 |
| 4¶ | F/45 | + | N | Gradual | Weight loss 4 pounds | OH | 3 | Y | Y | 2 | Y | Y | 9 severe | NA |
| 5‖ | F/54 | − | Y | Subacute | Weight loss 27 pounds; numbness of feet, face, and tongue | OH | 0 | N | Y | 2 | N Urgency | N | 9 severe | 78.14 |
| 6‖ | F/55 | − | Y | Gradual | None | OH | 3 | N | Y | 1 | N Urgency | N | 10 severe | 66.26 |

*Subacute = peak of autonomic failure within 3 months; gradual = gradual onset of chronic autoimmune autonomic ganglionopathy with the peak of autonomic failure after 3 months.
†0 = absent, 1 = dry eyes, 2 = dry mouth, 3 = both dry eyes and dry mouth.
‡0 = normal, 1 = constipation, 2 = severe constipation, 3 = persistent diarrhea.
§CN = cholinergic neuropathy: patients with at least three of four parasympathetic/enteric symptoms (sicca complex, abnormal pupil response to light, upper gastrointestinal symptoms, or neurogenic bladder).
¶Patient with positive acetylcholine receptor binding antibodies and modulating antibodies.
‖Patient with somatic fibers involvement (see EMG/nerve conduction studies section for details).
AB = ganglionic $\alpha_3$ acetylcholine receptor antibody; AE = antecedent event; OI = orthostatic intolerance; OH = orthostatic hypotension; UGI = upper gastrointestinal tract symptoms; LGI = lower gastrointestinal tract symptoms; CASS = Composite Autonomic Severity Score (1–3: mild autonomic failure; 4–6: moderate autonomic failure; 7–10: severe autonomic failure); COMPASS = Composite Autonomic Symptom Score; NA = not applicable.

dysautonomia.[2,3] This underlying immune-mediated pathogenesis in AAG has led to individual case reports showing clinical improvement with the use of immunotherapy including plasma exchange (PE), corticosteroids, and IV immunoglobulin (IVIg).[5-11] The clinical presentation, disease progression, and autonomic function tests do not distinguish between seropositive and seronegative putative AAG patients,[3] and some individual seronegative putative AAG patients respond to immunotherapy as well (P.A.L., unpublished observations). This observation suggests that the clinical phenotype of AAG, persistent severe autonomic failure, unassociated with ganglionic AChR antibodies could have another underlying autoimmune etiology and may respond to immunotherapy.

The aim of our study is to evaluate the efficacy of IVIg, PE, and immunosuppressants alone or in combination therapy in both seropositive and seronegative putative AAG patients.

## METHODS

**Patients.** We studied six patients with a clinical diagnosis of AAG. Patients with dysfunction of the sympathetic, parasympathetic, and enteric nervous systems with a ganglionic AChR autoantibody titer of >0.05 nmol/L prior to treatment were defined as having antibody-positive AAG.[2] In the absence of a confirmatory ganglionic antibody titer, patients with idiopathic pandysautonomia were required to have the following characteristics to be considered seronegative putative AAG: 1) orthostatic hypotension, defined as a systolic blood pressure reduction of ≥30 mm Hg or mean blood pressure reduction of ≥20 mm Hg occurring within 3 minutes of head-up tilt[2]; 2) significant gastrointestinal symptoms with predominant upper gastrointestinal dysmotility; and 3) severe autonomic dysfunction on standardized autonomic testing (Composite Autonomic Severity Score ≥7; see the corresponding section under Methods for details).

Additional criteria suggestive of seronegative putative AAG include pupillary involvement, prior antecedent event (i.e., viral illness), evidence of tissue inflammation (i.e., nerve, sweat gland), and subacute onset. Onset was defined as the time to peak autonomic dysfunction (subacute <3 months, gradual >3 months).

Comprehensive clinical, hematologic, biochemical, and serologic assessments of all patients were performed at baseline. Patients with known causes of autonomic failure including multiple system atrophy, diabetes, amyloidosis, rheumatologic disorders, and known malignancies were excluded. All the patients but one (case 4, table 1) were free of any other neuronal autoantibody on standard paraneoplastic antibody panels (Mayo Clinic, Rochester, MN).

Our sample comprises a prospective evaluation of four consecutive patients (cases 1, 2, 5, and 6) and a retrospective evaluation of the clinical records involving two patients (cases 3 and 4). All patients received a baseline assessment comprising autonomic function tests (autonomic reflex screen, thermoregulatory sweat test [TST], plasma catecholamine levels, determination of $\alpha3$ ganglionic AChR autoantibody level), electromyography, and nerve conduction studies (EMG/nerve conduction studies [NCS]). Patients also completed autonomic symptom profile (ASP) from which is derived a numerical score (Composite Autonomic Symptom Score [COMPASS]). All patients had inadequate responses to current symptomatic treatment for orthostatic hypotension including midodrine, pyridostigmine bromide, and fludrocortisone acetate.

After each course of IVIg or PE or during maintenance immunosuppressive therapy, patients underwent repeat autonomic function tests and ganglionic AChR antibody testing. The self-completed CCS was also obtained from patients prospectively evaluated (cases 1, 2, 5, and 6). This study was approved by the

Mayo Clinic Institutional Review Board. Informed consent was obtained from all participating patients.

**Autonomic evaluation.** ***Ganglionic AChR autoantibody.*** Autoantibodies binding to neuronal ganglionic AChR were detected by means of an immunoprecipitation assay as previously described.[4] Serum samples for antibody studies were collected before, weekly while the patient was under treatment, and after treatment. The upper limit of the normal range in serum is 0.05 nmol per liter as previously described.[4]

***Autonomic reflex screen.*** Quantitative sudomotor axon reflex test (QSART) evaluated the postganglionic sympathetic sudomotor axon[12] and the sweat response was recorded routinely from four sites (forearm, three leg sites). Control values were derived from studies on 223 healthy subjects aged 10–83 years.[13] Heart rate response to deep breathing (HR_db) and Valsalva ratio were used to evaluate cardiovagal function.[13] The control values were based on 157 healthy subjects aged 10-83 years.[13] Cardiovascular adrenergic function was evaluated by the BP and heart rate response to the Valsalva maneuver and head-up tilt. Beat-to-beat BP was monitored continuously (Finapres Monitor; Ohmeda, Englewood, CO).[14]

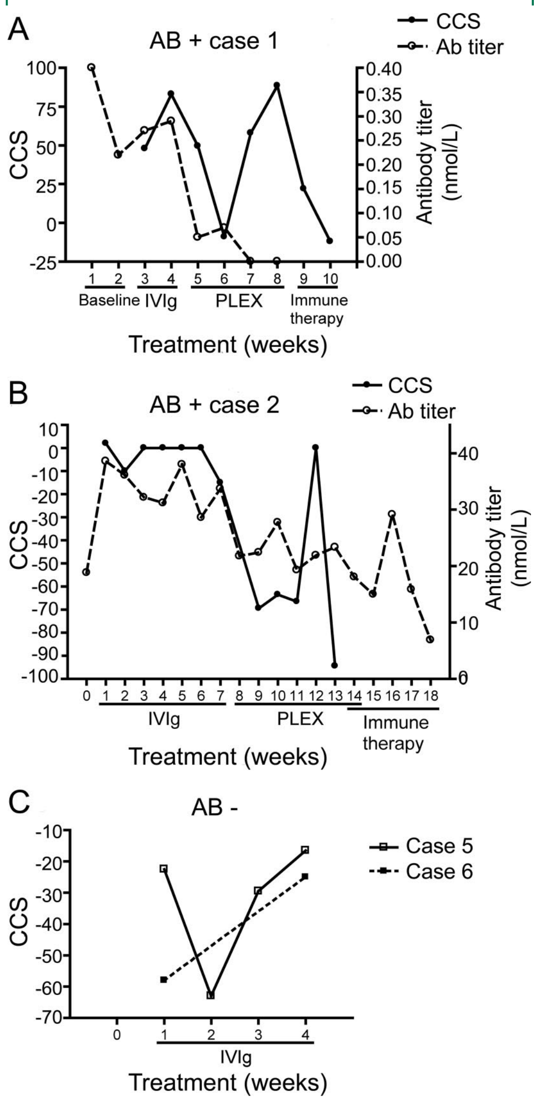
Composite Autonomic Severity Score (CASS) is derived from the autonomic reflex screen as previously described.[15] CASS provides an evaluation of severity and distribution of autonomic failure. The 10-point total CASS score is divided into three subscores: sudomotor (CASS-sudomotor; range 0–3), cardiovagal (CASS-cardiovagal; range 0–3), and adrenergic (CASS-adrenergic; range 0–4). Each score is normalized for confounding effects of age and gender.[13] Patients with autonomic failure were graded as follows: 1–3, mild autonomic failure; 4–6, moderate autonomic failure; and 7–10, severe autonomic failure.[15]

***Thermoregulatory sweat test.*** The TST assesses the pattern of sweat loss and provides a quantitative evaluation of percent of anterior body surface anhidrosis. The combined use of QSART and TST can help to define the site of lesion.[16] The TST was conducted in a heat cabinet and sweating was demonstrated by an indicator powder, and the percentage of anhidrosis on the anterior body surface was calculated from images created from digital photographs of the sweat distribution. Results were expressed as the percentage of body surface area that did not sweat (100% indicates complete anhidrosis).[17]

**Questionnaire.** ASP is a validated self-report instrument to assess autonomic symptoms, from which is derived a score (COMPASS). It provides an index of the severity and distribution of autonomic dysfunction. It yields one total score of overall severity of autonomic symptoms and 11 weighted subscale scores that assess severity of symptoms within the following domains: orthostatic intolerance, sexual failure (men only), bladder dysfunction, diarrhea, constipation, upper gastrointestinal (GI) tract symptoms, secretomotor dysfunction, sleep dysfunction, vasomotor symptoms, pupillomotor symptoms, and reflex syncope. COMPASS has been shown to correlate with CASS.[18]

COMPASS Change Score (CCS) is a self-completed questionnaire based on selected COMPASS domains (n = 7) to assess the change in autonomic symptoms during treatment. Thirty questions assess change of following autonomic domains: orthostatic, secretomotor, male sexual dysfunction, urinary, GI (including gastroparesis, diarrhea, and constipation), pupillomotor, vasomotor, and sleep function, with a maximum/minimal score for women of ±190, positive score indicating worsening and negative score improvement of autonomic symptoms (figure). In serial CCS, the score is referred to the improvement or worsening of autonomic symptoms after the prior treatment.

**Figure** **Immunotherapy of autoimmune autonomic ganglionopathy**




The effects of IV immunoglobulin (IVIg), plasma exchange (PLEX), and other immune therapies on autonomic symptomatology in both antibody-positive (AB+) and antibody-negative (AB−) patients. Autonomic symptoms, as measured by the COMPASS Change Scale (CCS), are shown for both AB+ patients (A and B) and AB− patients (C). Positive scores indicate worsening and negative scores improvement of autonomic symptoms. Corresponding ganglionic antibody titers are shown for both AB+ cases (A and B).

**Treatment.** ***IV immunoglobulin.*** All patients but one (case 6) were treated with standard doses of IVIg (0.2–1 g/Kg per dose; individual treatment regimens are specified in table 2) as first-line therapy considering it is reported to have less side effects and is efficacious in other autoimmune neurologic disorders as well as PE.

In the event that the patient did not respond to IVIg (no improvement of autonomic symptoms) or in the event that the patient had a transient improvement of autonomic symptoms, the patient was started on PE treatment. This was followed by

Table 2 Therapy regimen and clinical outcome

| Case | Therapy (dose/interval) | Outcome |
|---|---|---|
| 1 | IVIg, 0.4 g/kg body weight, 2x/wk for 2 wk | No benefit |
| | PE, 2x/wk for 4 wk, + prednisone, 80 mg/d for 6 wk | Patient complained of persistent autonomic symptoms; antibody level decreased to normal value |
| | Myc, 1,000 mg, 2x/d for 3 mo | Permanent and complete recovery |
| 2 | IVIg, 0.4 g/kg body weight, 2x/wk for 7 wk | Mild improvement of upper GI symptoms; patient still complained of several autonomic symptoms |
| | PE, 3x/wk for 2 wk, then 1x/wk for 3 wk | Transient marked improvement: pupil size became normal; improvement of bladder and bowel function |
| | PE, 1 each wk for 1 wk, + Aza, 100 mg/d; 2 mo | No benefit |
| | Myc, 1,000 mg, 2x/d for 1 y | Progressive improvement of GI symptoms, OI, bladder function; marked reduction of antibody level (see table 4) |
| 3* | IVIg, 0.4 g/kg body weight for 4 consecutive d for 3 wk, then once for a wk | Improvement of bladder function and OI, no dry eyes after IVIg; persistent dry mouth |
| 4* | IVIg, 1 g/kg body weight for 2 consecutive d; then 0.2 g/kg body weight once weekly for 3 mo; then 0.2 g/kg body weight every 2 wk for 3 mo; then 0.2 g/kg body weight 1x/mo for 14 mo | Improvement of bladder, bowel, sweating functions and pupillary response to light; persistent OI symptoms; several relapses |
| | IVIg, 0.2 g/kg body weight 1x/mo for 2 y, + Aza, 150 mg/d | Stable clinical condition, no relapses |
| 5 | IVIg, 0.4 g/kg body weight, 1x/wk for 4 wk | Marked improvement of OI; no numbness in the feet, normal bowel function; vomiting stopped, nausea resolved |
| 6 | Prednisone, 100 mg/d for 4 wk | No benefit |
| | Cyclophosphamide, 3 mo | No benefit |
| | IVIg, 0.4 g/kg body weight, 2x/wk for 4 wk; then 1x/mo for 3 mo; then 2x/mo for 8 mo | Improvement of OH, sweating, and somatic impairment; normal bladder function; resolved sicca syndrome |
| | IVIg, 0.4 g/kg body weight, 2x/mo for 1 year, + Myc, 1,000 mg 2x/d for 1 y | Normal blood pressure control, normal GI function, stable clinical condition, no relapses |
| | Prednisone, 60 mg alternate d, 1 y | |

IVIg = IV immunoglobulin; PE = plasma exchange; Myc = mycophenolate mofetil; GI = gastrointestinal; Aza = azathioprine; OI = orthostatic intolerance.

immunosuppressants agents if PE alone was not enough to reach a stabilized clinical improvement.

***Plasma exchange.*** Approximately three liters of plasma were removed for treatment per session. Plasma volume was replaced at a ratio of 1:1. The replacement fluid consisted of 5% purified human albumin in saline using partial heparin as the anticoagulant. For hemostatic reasons, fresh-frozen plasma was included as part of the replacement fluid within a 24- to 48-hour period following central line placement. PE was performed if the patient did not respond to IVIg. Patients underwent repeated courses of PE; each treatment consisted of PE on two or three consecutive days. The frequency and duration of PE was decided on clinical judgment.

***Immunosuppressive therapy.*** IVIg or PE courses were followed by immunosuppressive therapy in the event that patients did not have benefit from IVIg or PE alone or if they experienced a transient clinical recovery.

**RESULTS** We enrolled six patients with AAG (six women, mean ages 49.3 ± 10.6 years): four patients were autoantibody positive (AB+) and two were autoantibody negative (AB−). Clinical and autonomic characteristics in our patients are listed in table 1.

**Autonomic symptom profile.** Five patients completed the ASP: mean total score was 73.6 (SD 11.9) (table 3), significantly higher than an age- and gender-matched normal control group[19] (table 3). An impairment of several domains of autonomic symptoms was present, as listed in table 3. In this table, each value resulting in upper limit or abnormal range is indicated.

**EMG/NCS.** Five patients underwent EMG/NCS studies: normal findings were present in three patients (cases 1, 3, and 4) and a somatic neuropathy was present in two patients (cases 5 and 6). Case 5 had a right trigeminal neuropathy and a mild length-dependent axonal neuropathy of the lower extremities. In Case 6, the EMG/NCS studies were unremarkable at the onset of her symptoms but 4 months later, in parallel with the worsening of her symptoms, showed an axonal length-dependent sensorimotor neuropathy.

**Therapy.** All patients but one (case 6) were treated with IVIg as first-line treatment; in two patients (cases 3 and 5), this treatment allowed a prolonged improvement of the autonomic symptoms. The other four patients needed to continue the treatment adding PE or an immunosuppressant agent to reach a sustained improvement of autonomic symptoms (tables 2 and 4). However, all patients showed clinical improvement after treatment as follows (tables 2 and 4): one patient (case 1) showed progressive and complete improvement in AAG in response to PE followed by mycophenolate mofetil; one patient (case 2) showed the largest improvement of orthostatic intolerance and complete recovery of GI function with PE followed by mycophenolate mofetil. These two patients reported no clinical improvement with IVIg alone. Two patients (cases 3 and 5) reported marked improvement in orthostatic intolerance and bowel and bladder function with IVIg alone (see tables 2 and 4 for details). One patient (case 4) had improvement of bladder and bowel functions, pupillary response to light, and sweating with IVIg but had several relapses before her condition stabilized with maintenance therapy with IVIg and azathioprine. One patient (case 6) reported improvement of OH, sweating, bladder function, and somatic involvement with IVIg and continued to improve with the addition of myco-

Table 3 Autonomic symptom profile

| Autonomic symptom profile | Maximal score (normal range) | Case 1 | Case 2 | Case 3 | Case 5 | Case 6 |
|---|---|---|---|---|---|---|
| Orthostatic intolerance | 40 (0–30) | 37.5* | 40* | 32.5* | 35* | 32.5* |
| Bladder disorder | 20 (0–12) | 10 | 4 | 12* | 0 | 4 |
| Diarrhea | 20 (0–16) | 0 | 0 | 0 | 4 | 0 |
| Gastroparesis | 10 (0–6.7) | 3.34 | 10* | 1.67 | 8.35* | 3.34 |
| Secretory dysfunction | 20 (0–12.3) | 13.5* | 6 | 3 | 13.5* | 10.5 |
| Constipation | 10 (0–7.1) | 9* | 0 | 4.5 | 0 | 0 |
| Vasomotor | 10 (0–6.3) | 6.3* | 0 | 4.41 | 5.04 | 5.67 |
| Pupillomotor | 5 (0–2.7) | 5* | 4.5* | 2.5 | 3 | 1.5 |
| Syncope | 20 (0–4) | 4* | 4* | 0 | 4* | 8* |
| Sleep disorder | 15 (0–8.3) | 3.75 | 0 | 2.25 | 5.25 | 0.75 |
| Total score | 170 (0–44.9) | 92.39* | 68.5* | 62.83* | 78.14* | 66.26* |

The sexual failure subscale (which was completed by men only) was excluded in this study because all patients were female.
*Values resulting in upper limit or abnormal range, suggesting an impairment of the relative autonomic domain.

phenolate mofetil. She did not respond to earlier treatment with prednisone or cyclophosphamide.

**Autonomic function tests.** ***Sudomotor function.*** QSART was abnormal in five of six patients prior to treatment. QSART patterns were heterogeneous: four patients had widespread postganglionic sympathetic sudomotor impairment, patchy loss in one, and normal QSART in one (table 4). Treatment resulted in an improvement of QSART in four of the five patients with sudomotor impairment (table 4). Mean CASS-sudomotor score was 2.3 (SD 1.2) before treatment and 2.1 (SD 1.09) after treatment.

TST was abnormal in all patients. Patterns of abnormalities ranged from distal or focal anhidrosis to global anhidrosis (≥80% anhidrosis) with a mean value of 55.5% (SD 30.9). Therapy resulted in improvement of sweat distribution in four of six patients (table 4).

***Cardiovascular adrenergic function.*** CASS-adrenergic was severely impaired with a mean of 3.3 (SD 1.63). After treatment, mean CASS-adrenergic score was 3.1 (SD 1.60).

***Cardiovagal function.*** CASS-cardiovagal was moderately impaired with a mean of 2 (SD 0.63). After treatment, mean CASS-cardiovagal was 1.8 (SD 0.75).

Four patients had severe autonomic failure, one had moderate, and one had mild autonomic failure. Mean CASS total score of 7.6 (SD 2.65) indicated severe generalized autonomic failure. CASS total score after the treatment improved in three patients (case 1, 3→2; case 5, 9→7; case 6, 10→7). The mean CASS total score after the treatment was 7 (SD 2.6).

Ganglionic AChR autoantibody level in seropositive patients reverted to normal values after treatment in one patient (case 1) and remained elevated in the other three patients (cases 2, 3, and 4), with a substantial fall in all of them (table 4).

***COMPASS Change Score.*** All prospectively evaluated patients (cases 1, 2, 5, and 6) showed improvement of autonomic symptoms as measured by CCS (figure). Case 1 reported a mild improvement after the second course of PE and after immunosuppressive therapy with mycophenolate mofetil. Case 2 reported the most improvement after PE followed by immunosuppressive therapy with mycophenolate mofetil. Cases 5 and 6 reported improvement after IVIg alone.

**DISCUSSION** We report six patients with AAG (four ganglionic antibody positive and two seronegative putative AAG cases) who underwent immunotherapy with prospective and serial measurements of autonomic function and symptoms using validated tests and instruments. The present report highlights the heterogeneity of involvement and response to treatment. One consistent feature in patients with seropositive AAG is cholinergic and especially sudomotor neuropathy.

There is also consistently abnormal QSART and TST, emphasizing the value of TST%, which provides an index of the distribution of anhidrosis. After treatment, TST and QSART improved in four patients. Considering that QSART evaluates postganglionic sudomotor fibers,[12] these findings suggest that the site of lesion in those patients involves the postganglionic sympathetic sudomotor neuron (from ganglion to nerve terminal) or the sweat gland itself.[16]

The abnormality demonstrated on QSART could be a result of functional failure in the transmission of

**Table 4** Autonomic functional tests at baseline and after therapy

| Measure | Case 1 | | Case 2 | | Case 3 | | Case 4 | | | Case 5 | | Case 6 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Pre-therapy | Post-therapy | Pre-therapy | Post-therapy | Pre-therapy | Post-therapy | Pre-therapy | Post-IVIg therapy | Post-IVIg + Aza | Pre-therapy | Post-therapy | Pre-therapy | Post-therapy |
| **Antibody levels, nmol/L** | 0.40 | 0* | 18.8 | 6.86* | High (no exact titer) | 0.35 | 0.99 | 11.92 | 1.74* | 0 | | 0 | |
| **CASS total score** | 3 | 2 | 9 | 9 | 6 | 8 | 9 | 9 | | 9 | 7 | 10 | 7 |
| **QSART_FA** | 0.57 | 2.41* | 0.03 | 0.18* | 0.81 | 0.43 | 0.18 | 0.06 | | 0 | 0.27* | 0 | 0 |
| **QSART_PL** | 0.03 | 0.27* | 0.02 | 0.21* | 0.56 | 0.48 | 0 | 0.06* | | 0.19 | 0.44* | 0 | 0 |
| **QSART_DL** | 0.11 | 0.65* | 0.02 | 0 | 1.69 | 1.17 | 0 | 0.09* | | 0 | 0.61* | 0 | 0 |
| **QSART_Ft** | 0.59 | 0.4 | 0 | 0.05* | 0.50 | 0.16 | 0 | 0.21* | | 0.05 | 0.09* | 0.08 | 0 |
| **TST%** | 44% | 3%* | 35% | 20%* | 11% | 8% | 85% | 10%* | | 91% | 90% | 67% | 56%* |
| **VR** | 1.53 | 1.59* | 1.08 | 1.06 | 1 | 1 | 1.09 | 1.13* | | 1.18 | 1.31* | 1.19 | 1.65* |
| **$HR_{db}$** | 9 | 6 | 6 | 7.5* | 4.4 | 3.7 | 2.7 | 4.4* | | 5.7 | 4.3 | 2.3 | 4.3* |
| **Supine BP, mm Hg** | 124/82 | 130/74 | 136/88 | 130/86 | 124/76 | 130/80 | 134/86 | 184/114 | | 168/90 | 160/88 | 142/80 | 126/74* |
| **Standing BP, mm Hg** | 126/80 | 126/78 | 62/46 | 64/NA | 90/68† | 64/58† | 52/NA syncope | 120/96* | | NA, syncope | 72/56* | 92/66 | 126/72* |

The table shows the autonomic functional test before and after treatment.
*Improvement for each test when it is present.
†At 1 minute of head-up tilt.
IVIg = IV immunoglobulin; Aza = azathioprine; CASS = Composite Autonomic Severity Score (1–3: mild autonomic failure; 4–6: moderate autonomic failure; 7–10: severe autonomic failure); QSART = quantitative sudomotor axon reflex test volume (mL/sq cm); FA = forearm; PL = proximal leg; DL = distal leg; Ft = foot; TST% = thermoregulatory sweat test, % of anhidrosis; VR = Valsalva ratio; $HR_{db}$ = heart rate response to deep breathing; BP = blood pressure; NA = not applicable.

acetylcholine to cholinergic receptors including the most distal site of the sudomotor nerve terminal, the site that is stimulated by ACh during QSART.

We can speculate that AAG may be caused not only by ganglionic $\alpha 3$ AChR antibodies but also by other unknown antibody and that the postganglionic sympathetic pathways could be involved by another immunologic blockade, potentially reversible.

Although cholinergic sudomotor involvement is the rule in antibody-positive patients, patients differ in severity and distribution of deficits. CASS captures sudomotor, adrenergic, and cardiovagal deficits but ignores important areas such as bladder, bowel, and pupillary functions. This is demonstrated by case 1, who had relatively low CASS total score (CASS total was 3) with rapid improvement in sweating during treatment but with worsening of autonomic symptoms score (CCS), reflecting worsening involvement of other autonomic domains. The case emphasizes the need for a comprehensive instrument to cover all domains of dysautonomia.

Owing to the rarity of the disease, we undertook these studies to obtain preliminary data on efficacy of PE or IVIg as first-line therapy and to assess the value of combined therapy. Previous anecdotal observations[5-11] and our results suggest that IVIg, PE, and a combined therapy might be efficacious in treating AAG. Clearly, a placebo-controlled blinded clinical trial will be necessary to adequately prove efficacy.

In contrast to most immune-mediated neuropathies, where the putative mechanism is not known, AAG is due to ganglionic AChR antibody. This situation lends itself to a more mechanistic approach to immunotherapy. In addition, our study shows that seronegative putative AAG patients respond to immunomodulatory therapy as well. This suggests the need to treat patients with AAG phenotype even if seronegative for ganglionic AChR antibodies, as occurs in other autoimmune neurologic disorders like myasthenia gravis.[20,21]

In our patients, improvement in symptoms and deficits occurred with treatment with considerable heterogeneity in pattern of response. Some patients with AAG, whether seropositive or seronegative, respond to treatment with IVIg or PE, although when used as a single agent, subsequent treatments are required in most relapsing patients to maintain the improvement.

The more severely affect patients who did not respond to PE or IVIg monotherapy did benefit from a combined therapy adding immunosuppressant agents and seem to require prolonged immunotherapy for sustained clinical improvement.

Considering that the mechanisms of action among current treatments do not typically overlap, the use of a combination therapy, adding novel immunomodulatory drugs such as mycophenolate mofetil or rituximab, may increase the efficacy and provide a longer duration of clinical improvement. Those drugs could be a new promising treatment approach to this disorder.

## MEDICATIONS AND MEDICAL DEVICES

Azathioprine (Imuran®; Faro Pharmaceuticals, Houston, TX); cyclophosphamide (Cytoxan®; Bristol-Myers Squibb, Princeton, NJ); Finapres Monitor (Ohmeda, Englewood, CO); fludrocortisone acetate (Florinef®; Apothecon, Princeton, NJ); immune globulin (Sandoglobulin®; Novartis Pharmaceuticals, East Hanover, NJ); midodrine (Proamatine®; Shire US Inc., Newport, KY); mycophenolate mofetil (CellCept®; Roche Laboratories Inc., Nutley, NJ); prednisone (Deltasone®; Upjohn); pyridostigmine bromide (Mestinon®; Valeant Pharmaceuticals North America, Aliso Viejo, CA).

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